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Word Retrieval Learning Modulates Right Frontal Cortex in Patients with Left Frontal Damage

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Summary

Previous studies have suggested that recovery or compensation of language function after a lesion in the left hemisphere may depend on mechanisms in the right hemisphere. However, a direct relationship between performance and right hemisphere activity has not been established. Here, we show that patients with left frontal lesions and partially recovered aphasia learn, at a normal rate, a novel word retrieval task that requires the damaged cortex. Verbal learning is accompanied by specific response decrements in right frontal and right occipital cortex, strongly supporting the compensatory role of the right hemisphere. Furthermore, responses in left occipital cortex are abnormal and not modulated by practice. These findings indicate that frontal cortex is a source of top-down signals during learning.

Introduction

Neuroimaging studies have implicated the left prefrontal cortex in the retrieval of words from long-term memory based on semantic or phonological cues presented by vision or audition (Buckner et al., 2000; Gabrieli et al., 1996; Petersen et al., 1988; Price, 2000; Thompson-Schill et al., 1999; Wise et al., 1991). Specifically, the left inferior frontal gyrus (IFG) is commonly recruited in conjunction with lateral temporal and ventral occipitotemporal regions (Buckner et al., 2000; Thompson-Schill et al., 1999). Different hypotheses have been advanced concerning the role of left IFG regions in language processing. These frontal regions may be involved in semantic processing (Gabrieli et al., 1996; Petersen and Fiez, 1993), a function traditionally associated with left temporal cortex (De Renzi et al., 1987; Hodges and Graham, 2001). Alternatively, they may play a role in response selection of lexical representations in temporal cortex (Thompson-Schill et al., 1999). Finally, these regions may be involved in the transformation of sounds into articulatory patterns (phonology-to-articulation) (Blumstein, 1995). Left IFG contains multiple separate functional regions that might be partially specialized for these different functions (Buckner et al., 1995b; Poldrack et al., 1999).

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We have used patients with chronic left IFG damage as an experimental model for understanding the neurobiology of language recovery after stroke. Acute damage to the left IFG and adjacent cortical (middle frontal gyrus, insula, ventral motor cortex, anterior superior temporal gyrus) and subcortical white matter regions produces a clinical syndrome characterized by nonfluent, agrammatic, telegraphic speech with relatively intact auditory comprehension except for complex morphosyntactic structures (Broca's aphasia). Broca's aphasia recovers to different degrees, depending on the amount of damage to adjacent cortical and subcortical regions (Alexander, 1997; Dronkers et al., 2000; Kertesz and McCabe, 1977). When the lesion is limited to the posterior left IFG (Broca's area), patients resolve to a milder aphasia like a transcortical motor or an anomic aphasia (Mohr et al., 1978).

We studied patients with left IFG lesions using word retrieval tasks. Word retrieval in response to semantic or phonological cues robustly drives this part of the brain and is specifically impaired by left-IFG damage (Rosen et al., 2000; Thompson-Schill et al., 1998). Thus, regardless of the precise role it plays, left IFG cortex is necessary for normal word retrieval. The relevance of these tasks to the study of frontal aphasia is supported by the anatomical overlap of regions of functional activation and regions of structural damage in aphasia (Alexander, 1997; Dronkers et al., 2000; Rosen et al., 2000). In addition, patients with Broca's aphasia have problems in both word fluency (Goodglass et al., 1964) and word retrieval (Rosen et al., 2000; Thompson-Schill et al., 1998). While these tasks probe only a fraction of the complex behavioral impairment of patients with aphasia, they represent a useful instrument to study behavioral and functional changes after frontal damage.

A long-held view is that language function after left hemisphere injury depends on right hemisphere mechanisms (Gowers, 1865; Wernicke, 1908). This was suggested early on by the disruptive effects of strokes in the right hemisphere on recovered/residual language after a first left hemisphere stroke (Basso et al., 1989) and by the disruption of residual language after transient anesthesia of the right hemisphere with sodium amobarbital in patients with left hemisphere lesions (Kinsbourne, 1971). More recently, numerous neuroimaging studies have reported activation of homologous contralateral cortex in partially recovered aphasic patients with frontal or temporal lesions (reviewed in Rijntjes and Weiller, 2002).

However, currently there is no direct physiological support for this hypothesis. It is unknown if right hemisphere activity recorded at the chronic stage in neuroimaging studies is truly compensatory, merely reflects task difficulty or effort, or is just epiphenomenal. Some have suggested that right hemisphere activity is dysfunctional and maladaptive (Belin et al., 1996; Karbe et al., 1998). This is a tricky problem because overall differences in task performance are always present between aphasics and controls and may always be invoked to explain differences in the pattern of brain activation.

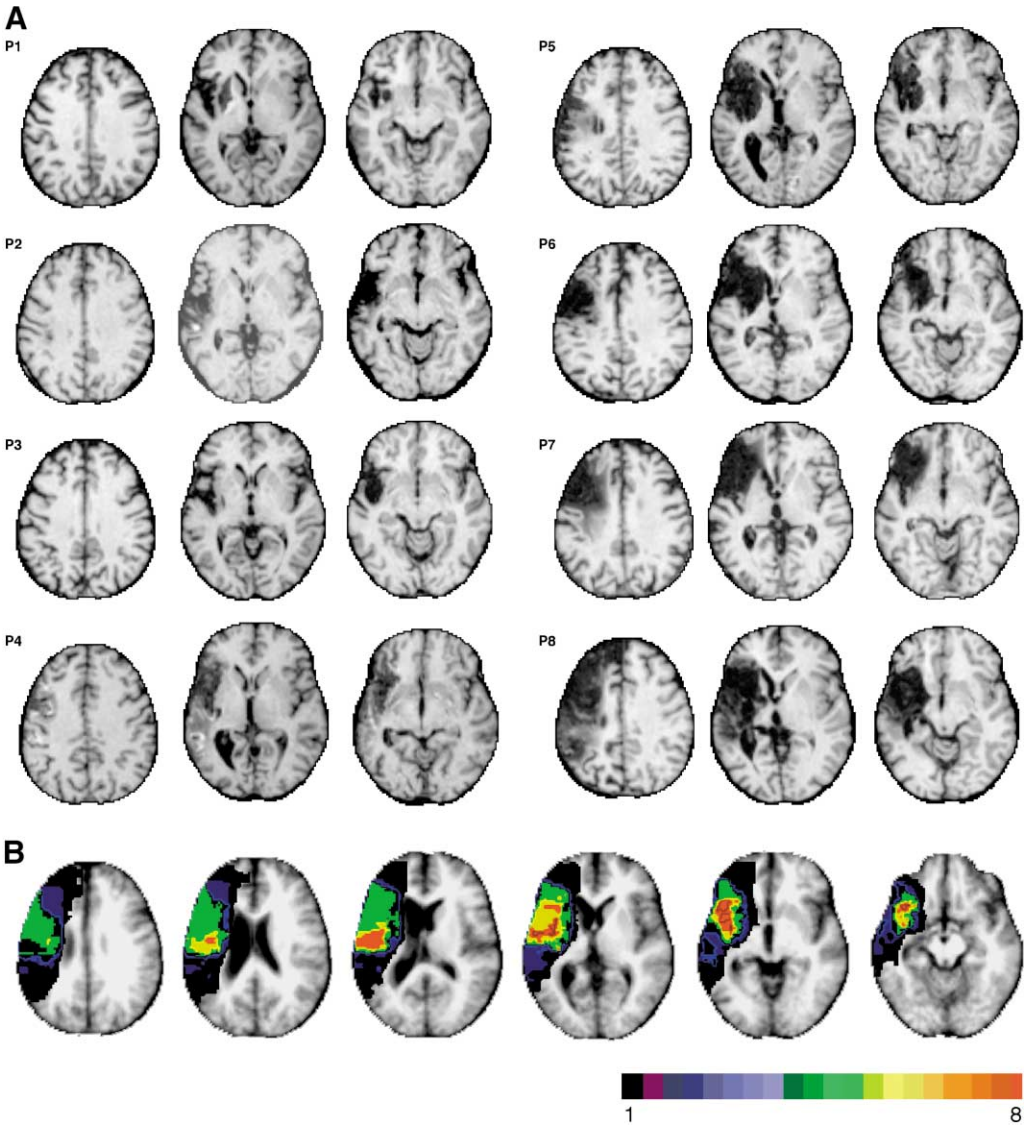

Figure 1. Lesion Anatomy

(A) Individual subjects. All subjects sustained an ischemic stroke that included the posterior left inferior frontal gyrus (IFG) and operculum (Broca's area).

(B) Average lesion density. The color scale indicates number of patients contributing to the average lesion image. The underlying greyscale image shows the average patient MP-RAGE.

Studies that have tried to correlate activity in right hemisphere regions with behavioral performance yielded conflicting results (Belin et al., 1996; Heiss et al., 1999; Karbe et al., 1998; Musso et al., 1999; Rosen et al., 2000), and none of those experiments measured brain activity and behavior simultaneously.

We tackled this problem by hypothesizing that if the right IFG is part of a compensatory system after left frontal damage, then it should manifest physiological modulations of activity analogous to those observed in the left IFG of the intact brain. When control subjects are repeatedly exposed to the same list of word stems and asked to generate a word in response to each stem, vocal reaction times speed up over list repetitions and selection of words become more stereotypical. These behavioral changes are accompanied by functional response decrements in left IFG and left occipito-temporal cortex that are independent of the input modality (auditory or visually, Buckner et al., 2000). Similar repetition effects have been reported in semantic tasks (Raichle et al., 1994; Thompson-Schill et al., 1999).

Under the hypothesis that the right IFG is compensating for processes carried out in left IFG, we predicted that subjects with left IFG damage should still improve their performance and that, correspondingly, activity in right IFG should show physiological response decrements with practice. Conversely, if right IFG activity is not compensatory, then subjects might not be able to learn the task or learn it but show response decrements elsewhere in the brain.

A second important issue addressed by this study is the functional interaction between frontal cortex and

Table 1. Standardized Language Assessment in Frontal Patients

WAB	P1	P4	P5	P6	P7	P8	BDAE	P2	P3
Initial deficit	Broca	Broca	Broca	Global	Global	Global		Mixed	N/A
AQ	84.4	67.6	66.5	89	74	67	Aphasia severity	4	
Classification	TM	TM	TM	Anomic	Anomic	Broca		Anomic	
Fluency	6	5	4	9	5	4	Fluency	8.67	
Repetition	8.2	7.1	8.9	8.6	8.3	6.4	Repetition	7	
Comprehension	10	6.7	9.45	10	8.8	8.15	Aud. Comp.	26.75	
Naming	9	8	4.9	7.9	6.9	7.8	Naming	49.67	

Abbreviations: WAB, Western Aphasia Battery; BDAE, Boston Diagnostic Aphasia Examination; P1–P8, patients 1–8; TM, transcordial motor. Initial diagnosis was based on clinical assessment. Standardized assessments were performed at the time of testing. P3 was not formally examined.

posterior cortical regions during learning. Response decrements during verbal learning have been observed in a variety of posterior cortical regions in parallel to frontal changes (Buckner et al., 2000; Raichle et al., 1994; Thompson-Schill et al., 1999). These posterior regions are normally recruited during processing of both visual and auditory words and are thought to be part of a semantic network for words and object processing (Alexander et al., 1989; Vandenberghe et al., 1996). One possibility is that response decrements in posterior regions during learning are independent of frontal influence and are related to the repetition of stimuli. Stimulus repetition is known to produce decrements in both neuronal activity and hemodynamic signals in occipito-temporal cortex (Buckner et al., 1998; Miller et al., 1996). This bottom-up hypothesis predicts that a frontal lesion should not influence responses and repetition effects in occipito-temporal cortex. Another possibility is that frontal cortex interacts with occipito-temporal cortex during learning. For example, frontal cortex might be involved in the selection of information from posterior representations (Thompson-Schill et al., 1999). A frontal lesion then would disrupt top-down processes and modulation of posterior regions.

Results

Fourteen age-matched controls and eight patients with a stroke centered in left IFG cortex near/at Broca's area at least 6 months prior (Figure 1) participated in the study. All patients were initially severely aphasic, but had recovered to a mild-to-moderate Broca's or anomic aphasia at the time of the experiment based on a standardized language assessment. All patients were impaired on measures of verbal fluency and word generation (Table 1).

The study consisted of two parts, a behavioral and an fMRI session during which subjects were asked to perform a word stem completion task. Subjects were shown 3-letter visual word stems (e.g., "COU") on a computer screen and asked to generate a word beginning with the same three letters (e.g., "couple") as quickly and accurately as possible. During the behavioral session subjects practiced the word stem completion on the same 40 stimuli list of word stems for seven consecutive blocks. The order of presentation of the word stem was randomized in each block. On the eighth block they were presented with a new list of words to verify that learning was item specific. Behavioral data were analyzed with a 1-between (controls, patients), 1-within (block order, 1-7) random effect ANOVA.

Compared to controls, patients were slower: vocal reaction times (RTs) were 1417 ms in patients and 1121 ms in controls, $F(1,20) = 6.59$, $p = 0.02$ (Figure 2A) and less accurate (percent correct was 66% in patients and 97% in controls, $F(1,20) = 41.26$, $p < 0.0001$(Figure 2B). However, both groups learned at a similar rate as measured by an overall decrement in vocal RT with practice [$F(1,7) = 10.85$, $p < 0.0001$] without a significant interaction between groups [$F(7,140) = 1.82$, $p =$ ns]. Vocal RTs decreased in patients from 1670 ms (first block) to 1264 ms (seventh block) and in controls from 1364 ms to 865 ms. Errors also decreased with practice [$F(1,7) = 16.73$, $p < 0.0001$], more so in patients than controls [$F(7,140) = 5.67$, $p < 0.0001$]. In patients, the percentage of accurate responses went from 59% on the first block to 73% on the seventh block. Controls were at ceiling with accurate responses from 95% to 99% (Figures 2A and 2B).

Another indicator of learning was the percentage of stereotypical completions, i.e., the percentage of words repeatedly used to complete the same word stem across blocks. Stereotypical completions increased over time in both groups [$F(5,5) = 26.3$, $p < 0.0001$]. They were higher in controls (mean = 77%) than in patients (mean = 57%) [$F(1,19) = 6.48$, $p = 0.02$], but the rate of increase across blocks was similar, as indicated by a nonsignificant interaction group-by-block order effect [$F(5,95) = 0.30$, $p =$ ns]. Patients generated the same words on 46% of the trials at the beginning of learning (block 2 versus 1) and on 64% of the trials at the end of practice (block 7 versus 6). Controls generated the same words on 65.5% (block 2 versus 1) and on 85.5% (block 7 versus 6) of the trials, respectively. Finally, learning was item specific because performance returned to baseline levels when a novel list of word stems was introduced (Figures 2A and 2B).

In functional magnetic resonance imaging (fMRI), subjects silently performed word stem completion during whole-brain measurement of blood oxygen level dependent (BOLD) signal. One set of word stems was presented over four consecutive (practice) fMRI runs; novel sets of word stems were presented in four additional runs (Figures 2C and 2D). To ensure that learning occurred in the covert condition, we measured (with the scanner off) overt performance before and after the practice fMRI runs. Patients were again slower [$F(1,20) = 10.77$, $p = 0.004$] and less accurate [$F(1,20) = 33.67$,

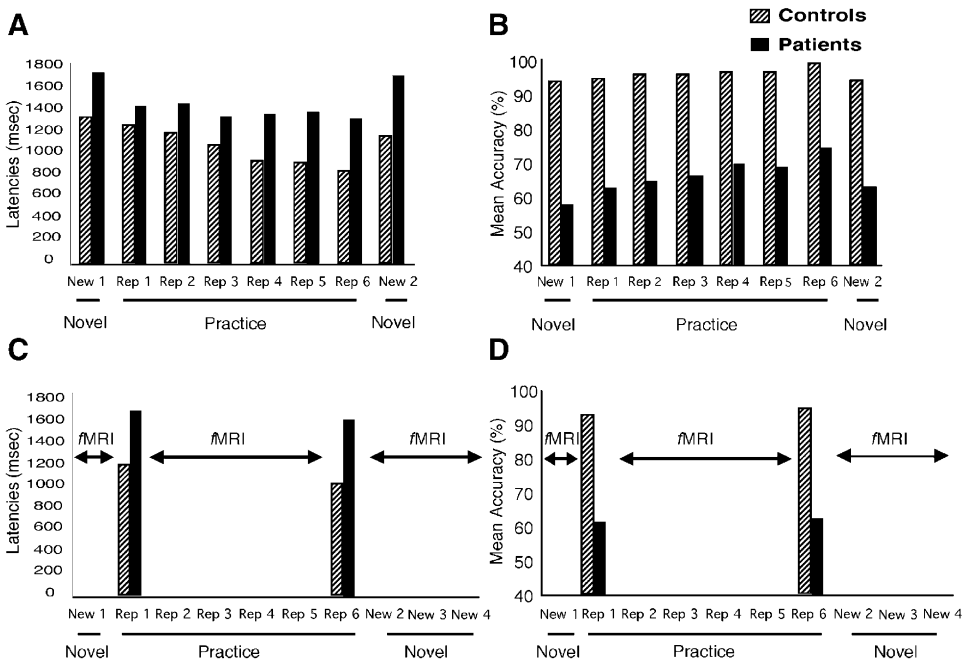

Figure 2. Subjects' Performance on the Word Stem Completion Task

Behavioral session (A and B). Vocal RTs (A) and mean accuracy (B) for controls (striped) and patients (black). Abbreviations: New, new list of word stems; Rep, repeated lists of word stems. fMRI session (C and D).

$p < 0.0001$] than controls. Both groups showed improvement with practice (RTs [$F(1,1) = 13.37$, $p = 0.002$]; errors [$F(1,1) = 3.29$, p = ns]), again without significant interaction between groups [(group-by-block order: RTs $F(1,20) = 2.13$, p = ns; errors $F(1,20) = 0.015$, p = ns) (Figures 2C and 2D)].

Figure 3 shows the group-average functional anatomy of the word stem completion task in controls and patients. Controls bilaterally activated occipital and parietal regions generally thought to mediate visual analysis. Controls also activated multiple frontal regions including the dorsal (BA 44/6) and the ventral portion of the IFG extending into the operculum (BA 44-45), SMA, and anterior cingulate cortex. Frontal activations were stronger and larger in the left hemisphere (Figure 3, top). These results confirm previous studies (Buckner et al., 2000, 1995a; Desmond et al., 1998; Ojemann et al., 1998).

The patients activated a similar cortical network ex-

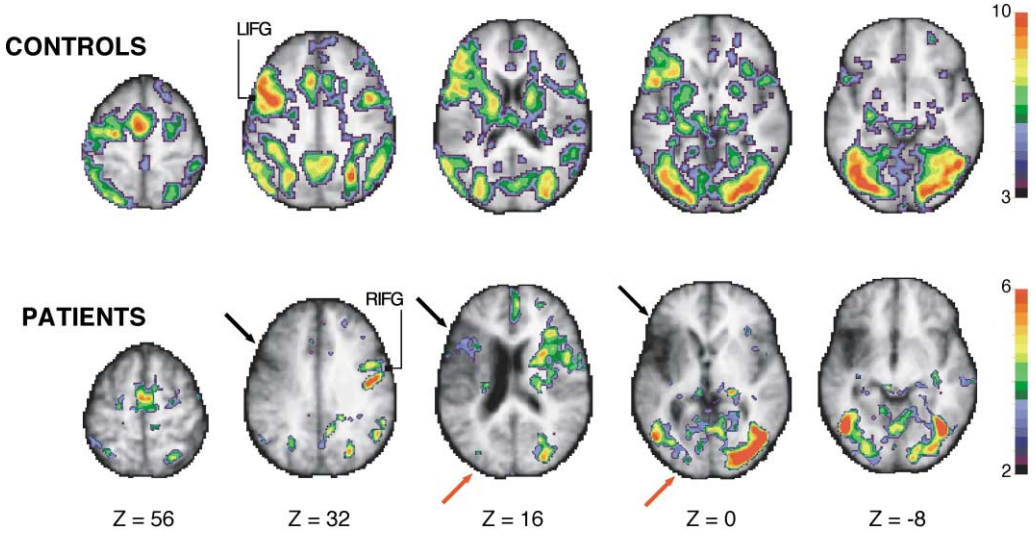

Figure 3. Functional Anatomy of Word Stem Completion in Controls and Patients

F map transformed to Z map (color scale in z values) corrected for multiple comparisons. The statistical maps show regions of BOLD signal change during word stem completion, independently of practice. Averaged functional data are coregistered with averaged anatomical MRI scans in each group. Black arrow, lack of activation in lesion. Red arrow, decrease activation in left dorsal occipital cortex in patients with left frontal lesion.

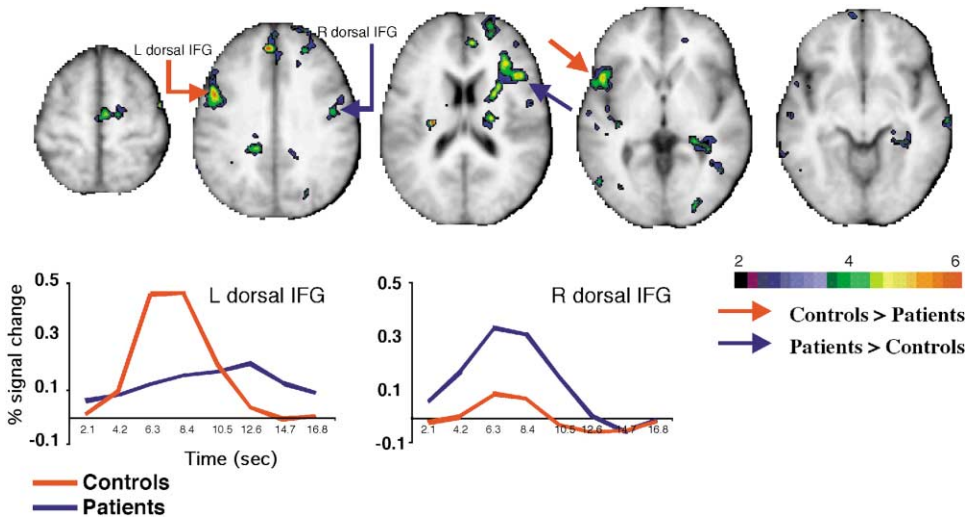

Figure 4. Differential BOLD Response during Word Stem Completion in Controls and Patients

F map transformed to Z map (color scale in z values), interaction of group (controls, patients) × MR frame. Slices are the same as in Figure 3. Red arrow indicates regions in which magnitude of BOLD signal was higher in controls than patients. Blue arrow indicates regions in which magnitude of BOLD signal was higher in patients than controls. Graphics show average BOLD timecourse for novel items timelocked to stimulus onset in the left and right dorsal IFG (z = 32) cortex. Y axis, percent signal change; X axis, time in seconds.

cept for three major differences (Figure 3, bottom). First, there was no significant activation in correspondence of the lesion or in the underlying basal ganglia and thalamus (black arrow). Second, the activation of left striate and dorsal exstrastriate cortex ipsilateral to the lesion was depressed (red arrow). Third, right frontal cortex was more strongly activated in patients than in controls (Figure 4). This qualitative impression was confirmed by the results of voxel-wise and regional group (controls, patients) × MR frame (1–8) ANOVAs. This analysis formally showed that several left frontal cortex (dorsal IFG, x, y, z = −45, −1, 40, $F(7,140) = 7.90$, $p < 0.0001$; ventral IFG, x, y, z = −47, 3, 32, $F(7,140) = 7.71$, $p < 0.0001$; frontal operculum, x, y, z = −47, 11, 4, $F(7,140) = 7.29$, $p < 0.0001$) were more active in the control group, whereas right frontal cortex (middle frontal gyrus, x, y, z = 33, 27, 22, $F(7,140) = 8.39$ $p < 0.0001$; dorsal IFG, x, y, z = 51, 1, 34, $F(97,140) = 4.17$, $p < 0.001$; anterior insula/frontal operculum, x, y, z = 27, 9, 14, $F(7,140) = 4.89$, $p < 0.0001$; ventral IFG, x, y, z = 41, 17, 18, $F(7,140) = 6.00$, $p < 0.0001$; Precentral, x, y, z = 47, −7, 54, $F(7,140) = 7.13$, $p < 0.0001$) was more active in the patient group (Figure 4). Hence, functional changes following left frontal damage include both an increased activation in contralateral frontal cortex and a reduction of activation in ipsilateral visual cortex.

Practice on word retrieval modulated BOLD responses in several cortical areas in both control and aphasic subjects. In control subjects, practice-related decrements were observed in left prefrontal cortex (dorsal IFG) (Figure 5A), bilateral extrastriate visual cortex (fusiform and lateral occipital complex) (Figure 5A), right middle frontal gyrus, SMA, and right lateral cerebellum (Table 2 for complete list). Importantly, no decrement was observed in right prefrontal cortex (dorsal IFG, $p = 0.12$, and ventral IFG, $p = 0.59$) (Figure 5A). Regions near primary visual cortex (e.g., right lingual gyrus) showed similar responses to novel and repeated stimuli, i.e., were not modulated by practice. These results confirm previous work using block designs (Buckner et al., 2000; Raichle et al., 1994).

In patients, practice-related decrements were largely confined to the right hemisphere, specifically to the right dorsal IFG, right fusiform cortex (Figure 5B), and right lateral occipital cortex. Importantly, these modulations were significantly stronger in the patient than the control group (1-between (controls, patients), 1-within (novel, repeat) regional ANOVA: right dorsal IFG, $F(1,20) = 5.41$, $p = 0.031$; right anterior fusiform, $F(1,20) = 4.98$, $p = 0.038$) (Figures 5A and 5B). These findings were confirmed by a voxel-wise ANOVA on group (controls, patients), practice (novel, repeat), and MR frame (1–8). As in controls, regions near primary visual cortex (e.g. right lingual gyrus) were not modulated by practice.

Furthermore, in marked contrast to control subjects, no practice-related modulation was observed in the left fusiform cortex ipsilateral to the lesion, an area that has been consistently associated with word retrieval learning and priming for both visual and auditory words (Buckner et al., 2000). In this region, the magnitude of the BOLD response was almost twice as strong as in controls, but it was not modulated by practice (compare left fusiform BOLD response in controls and patient, Figures 5A and 5B). Hence, left frontal damage causes both a relative deactivation of ipsilateral left dorsal visual cortex and an abnormally high nonselective activation of left ventral occipital (fusiform) cortex.

It was also possible to image practice-related decrements in single subjects (Figure 6). Practice-related decrements in right IFG occurred in all patients with larger frontal lesions and exclusive activation on the right during word retrieval (patients P4–P8) (Figure 6). In those patients with smaller lesions and both perilesional and right IFG activity (patients P1–P3), decrements were bilateral (Figure 6). It was not possible to determine whether the strength of practice-related modulation in

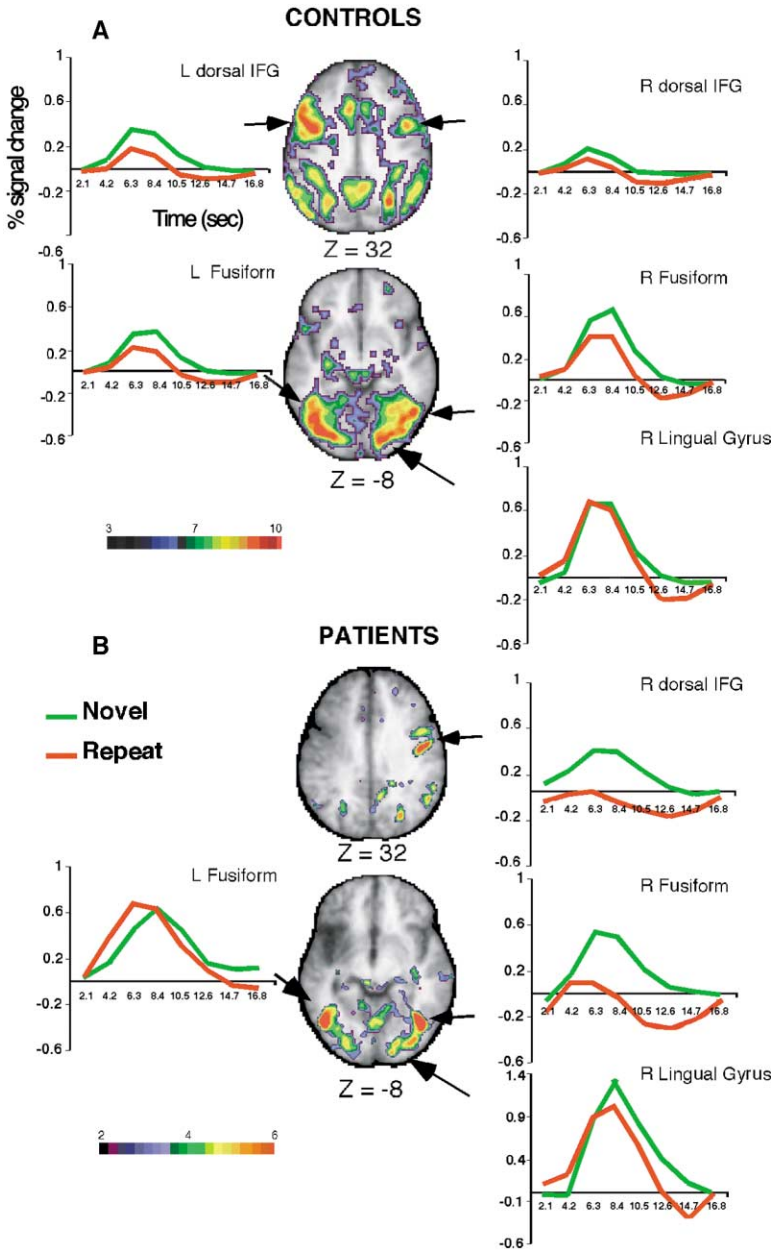

Figure 5. Practice-Related BOLD Modulation in Frontal and Occipital Cortex in Controls and Patients

F maps transformed to Z maps (color scale in z values) corrected for multiple comparisons, main effect of MR frame. Selected slices through frontal (IFG, z = 32) and occipital (fusiform, z = −8) cortex. Graphics show average BOLD time course for novel and repeat items timelocked to stimulus onset. Y axis, percent signal change; X axis, time in seconds.

right IFG and perilesional left IFG correlated with the size of the left frontal lesion because of low statistical power.

Interestingly, the patients (P1–P3) with perilesional activation (and smaller lesions) performed better overall on word stem completion. 1-between (patients with [P1–P3] and without [P4–P8] perilesional activity) 1-within (block order, 1–7) ANOVAs on accuracy or stereotypical responses showed that mean accuracy (83% versus 55.5%, $F(1,5) = 8.00$, $p = 0.037$) and frequency of stereotypical completions (75% versus 44%, $F(1,5) = 7.70$, $p = 0.039$) were higher in patients with than in those without perilesional activity. However, the rate of learning was comparable in the two groups. There was no significant interaction of patients with/without-by-block order on either measure [errors, $F(6,30) = 1.52$, $p =$ ns; stereotypical responses, $F(5,25) = 0.839$, $p =$ ns]. Reactions times were also not significantly different (with: 1365 versus 1503 ms, $t = -0.65$, $p =$ ns).

Discussion

Word Retrieval Learning in Left Frontal Patients

In this study, we show that aphasic patients with chronic structural damage of left IFG cortex and surrounding tissue learn novel associations between word stems and words at a fairly normal rate. Learning was manifested as a decrease of errors and vocal RTs on correct trials in both behavioral and fMRI session and as an increase in the number of stereotypical completions over time. The rate of decrement for RTs was similar in patients and controls in both behavioral and fMRI session. Verbal stereotypies also increased in both groups at a similar rate. Errors decreased more in patients than controls in

Table 2. Anatomical Regions with a Significant Practice Effect (Novel > Repeat Items) in Controls and Patients

Controls Region	X	Y	Z	Peak Z Score	Novel versus Repeat P Value
L dorsal IFG	−45	−3	38	5.98	0.002
L ventral IFG	−29	15	6	4.99	0.06
R MFG	41	27	20	4.91	0.001
L anterior fusiform	−37	−53	−18	7.22	0.02
R anterior fusiform	33	−47	−18	6.06	0.02
R posterior fusiform	39	−69	−10	6.81	0.002
R lateral occipital	23	−89	4	7.04	0.02
R lateral cerebellum	47	−55	−28	3.36	0.0002
L SMA	−5	−5	58	6.26	0.03
L Frontal Patients Region	**X**	**Y**	**Z**	**Peak Z Score**	**Novel versus Repeat P Value**
R dorsal IFG	43	−11	34	4.25	0.01
R posterior fusiform	37	−65	−8	5.12	0.04
R lateral occipital	25	−87	−2	5.84	0.001
R lingual	13	−95	−10	5.15	0.04
L MTG	−47	−69	−4	5.46	0.03

Anatomical name; x, y, z refer to Talairach atlas coordinates. Peak voxel z score on voxel-wise ANOVA (main effect: MR frame) assessing reliable activation during word stem completion. P value refers to significant interaction in regional ANOVA, MR frame × item (novel versus repeat), assessing reliable practice effect. Abbreviations: IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SMA, supplementary motor area; MTG, middle temporal gyrus.

the behavioral session (but not in the fMRI session), but this can be explained by the high accuracy of controls.

That patients and controls exhibited comparable RT decrements and change in the number of stereotypies with practice is significant given that word learning is generally thought to depend on the left IFG (Buckner et al., 2000; Raichle et al., 1994; Rosen et al., 2000; Thompson-Schill et al., 1998). Our data suggest that patients use alternative brain pathways and possibly processing strategies to learn a novel verbal task.

A critical issue for the interpretation of the imaging results is the nature and stage of processing at which this form of learning occurs. Is the association between a visual word stem and the retrieval of a single word a form of visuomotor learning, or does it depend on linguistic mechanisms? Does learning occur at the stage of stimulus analysis, lexical retrieval, or response selection? These questions are closely related to the normal contribution of left IFG to word retrieval and the interpretation of physiological response decrements in this part of cortex during word retrieval learning.

The best available evidence indicates that left IFG

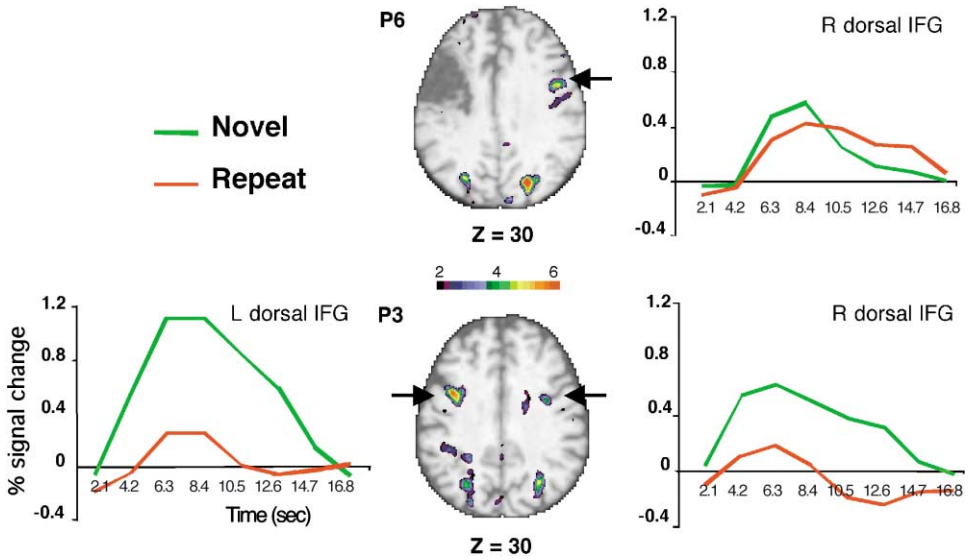

Figure 6. Practice-Related BOLD Modulation in Single Patients

F maps transformed to Z maps (color scale in z values) corrected for multiple comparisons, main effect of MR frame. Selected slices through frontal cortex (IFG, z = 30). Graphics show average BOLD time course for novel and repeat items timelocked to stimulus onset. Y axis: percent signal change; X axis, time in seconds. P6 with large frontal stroke activates exclusively the right IFG in which novel items produce stronger activation then repeat items. P3 with smaller more ventral lesion (not shown) activates both left and right IFG, and practice-related decrements are bilateral.

cortex is important for the selection of responses from competing lexical information, presumably stored posteriorly in temporal cortex (Thompson-Schill et al., 1999). Left IFG cortex is recruited during both semantically cued and phonologically cued word retrieval tasks (Buckner et al., 2000, 1995a; Gabrieli et al., 1996; Petersen et al., 1988; Price, 2000; Thompson-Schill et al., 1999; Wise et al., 1991), and its damage causes deficits on these tasks (Rosen et al., 2000; Thompson-Schill et al., 1998). More specifically, left IFG-damaged subjects seem unable to inhibit competing lexical items during word retrieval (Buckner et al., 1996; Thompson-Schill et al., 1998). Accordingly, left IFG cortex responds more strongly under conditions of increased competition between possibly retrieved items (Desmond et al., 1998; Thompson-Schill et al., 1999).

The need for response selection, however, decreases with practice. Learning of word stem completion and similar tasks is currently conceptualized in the theoretical framework of repetition priming (Tulving and Schacter, 1990). Repetition of the same inputs, retrieval, and output processes facilitates processing speed and strengthens stimulus-response association while concurrently decreasing the amount of evoked neural activity that becomes more selective and spatially confined (Rainer and Miller, 2000). Hence, response decrements in left prefrontal cortex may underlie either an increased efficiency of retrieval (semantic, phonological) processes (Gabrieli et al., 1998; Petersen and Fiez, 1993; Raichle et al., 1994), or a decreased need of selection as the competition between alternative responses decreases with practice (Thompson-Schill et al., 1999).

In the absence of a critical cortical module for response selection of lexical items, practice still induced normal behavioral improvement. As this form of learning requires the selection and retrieval of lexical information and not just the association of a visual stimulus with a motor response, then the implication is that compensatory brain pathways modulated by practice are also involved in lexical operations.

Frontal Mechanisms

In two previous reports, we showed that patients with left frontal damage centered on the IFG activate, to an abnormally high degree, homologous regions in right frontal cortex (dorsal and ventral IFG) during word stem completion (Buckner et al., 1996; Rosen et al., 2000). However, no correlation was established between verbal performance and activity in right IFG (Buckner et al., 1996; Rosen et al., 2000). Hence, it was difficult to decide whether activity in right frontal cortex was compensatory or just epiphenomenal, reflecting factors such as effort or task difficulty or recruitment of ineffective mechanisms. This limitation, we believe, is common to all published studies of aphasia recovery. Conflicting results have been obtained by correlating neuropsychological results with functional imaging data (Belin et al., 1996; Heiss et al., 1999; Karbe et al., 1998; Musso et al., 1999; Rosen et al., 2000), and no prior experiment has correlated behavior during fMRI and brain activity.

The novel finding here is that compensatory activity in right frontal cortex (dorsal IFG) decreases as performance improves during learning of word stem completion. The response modulation is specific because it occurred only in the aphasic group with left frontal damage. No practice-related decrements were observed in right frontal cortex in the control group. Moreover, when response decrements in right frontal cortex were directly compared between groups, they were significantly stronger in patients.

It is unlikely that response decrements in right frontal cortex reflect less task difficulty or effort. These explanations would predict a uniform decrease of activation throughout the brain. Rather, these modulations were localized to right frontal and occipital regions. Moreover, the specific pattern of modulation in the occipital lobe strongly argues against this possibility (see below). Finally, patients clearly found the task difficult even after repeated practice as indicated by high error rates and slow reaction times, which never reached control values.

The response decrement in right frontal cortex resembles the normal modulation induced by word retrieval practice in the left frontal cortex. Since the left frontal cortex is critical for normal performance of word retrieval, the present findings imply that activity in right frontal cortex correlates with, and likely mediates, the performance improvement after left frontal cortex damage. It also suggests that this activity compensates for the absence of left frontal cortex. These mechanisms may not be operative in controls in whom practice mainly modulates the left frontal lobe.

In addition, the degree of BOLD response attenuation in right frontal cortex of patients was significantly stronger than that observed in the left frontal cortex of controls. Similarly, the average response of right frontal cortex during word stem completion was significantly stronger than in controls. Such abnormal activation of homologous right frontal regions after left frontal damage has been now replicated in three separate studies (Buckner et al., 1996; Rosen et al., 2000, and this study). In Rosen et al., we proposed that this enhanced activation might reflect the loss of inhibitory or competitive mechanisms that normally regulate the level of activation in homologous cortical regions. A study by Konishi et al. (2001) found that left and right frontal regions are initially both recruited during word retrieval, but that over time activity on the right side decreases while activity on the left side remains elevated. It is possible, in the absence of left frontal cortex, that lack of competitive interaction between hemispheres produces an abnormal level of activation and abnormal practice-related modulation in right frontal cortex. The idea of reciprocal regulation of activity in homologous cortical regions is not novel; it has been proposed by theories addressing the functional roles of the callosal connections (Gazzaniga, 1970) and the behavioral competition between hemispheres (Kinsbourne, 1977).

The switch of practice-related modulations from the left to the right frontal cortex in patients with left frontal lesions may reflect a variety of mechanisms. One possibility is that activity in right frontal cortex reflects the recruitment of a novel pathway created by neural plasticity (e.g., by growth of new synapses) that allows this system to take over the set of functions originally localized in the left IFG. This possibility is unlikely for several reasons. Enhanced right-IFG responses have been observed acutely (within 24 hr) (Thulborn et al., 1999) and

subacutely (within 3 weeks) (Leitner et al., 2001, Soc. Neurosci. Abstr.; Rosen et al., 1998, Soc. Neurosci. Abstr.) after the onset of a left stroke. Such rapid adjustments are inconsistent with the growth of new anatomic pathways.

Another hypothesis, which we prefer, is a switch in processing strategies. For example, patients may have switched from a semantic-phonological strategy to a more visual (orthographic) strategy. Performance studies in normal (Balota, 1994) and split-brain subjects (Gazzaniga, 1983; Zaidel and Peters, 1981) as well as fMRI studies in normal volunteers (Brewer et al., 1998; Courtney et al., 1996; Kelley et al., 1998; Wagner et al., 1998) have demonstrated a differential sensitivity of the two hemispheres to these different lexical codes. Specifically, left and right dorsal IFG regions that are identical to those recruited during word stem completion and show compensatory activity in patients can be tightly regulated by stimulus materials in certain tasks. Left frontal responses predominate during the encoding of words; right frontal responses predominate during the encoding of non-nameable faces; but, bilateral responses occur during encoding of nameable objects (Kelley et al., 1998). Thus, it is possible that a visual strategy may allow normal learning despite a lower overall performance due to the disruption of semantic-phonological processors in the left prefrontal cortex.

Occipital Mechanisms

Another important result of this study is the demonstration that the integrity of frontal cortex is critical for normal response of visual cortex. Left frontal damage caused a reduction of normal activation in dorsal extrastriate regions as well as abnormally high activity in left ventral extrastriate regions with a disruption of learning-related response decrements. In addition, left frontal damage induced stronger than normal response decrement with practice in right occipital cortex that matched the modulation in right frontal cortex. Thus, left frontal damage produced specific changes in both ipsilesional occipital cortex and contralesional frontal and occipital cortex.

Disruption of neural activity in left occipital cortex cannot be explained by decreased sensory responsiveness to the visual stimuli. None of the patients had a visual field cut or damage of the optic pathways by anatomical MRI. Also, the stimuli generated abnormally strong nonselective activation of left fusiform cortex. This latter effect is reminiscent of the effect of frontal lesions on primary auditory and somatosensory evoked potentials (Knight et al., 1989; Yamaguchi and Knight, 1990). These electrical potentials are abnormally high in sensory cortices in the presence of ipsilateral frontal damage and may reflect the loss of a frontal inhibitory gating mechanism.

Also, practice-related modulations in visual cortex cannot be explained by pure perceptual priming due to repeated presentation of the same visual items (Buckner et al., 1998; Miller and Desimone, 1994). If response decrements during word stem completion were purely due to stimulus repetition, then activity in left occipital cortex should have not been influenced by ipsilateral frontal damage. Analogously, the strength of the modulation in right visual cortex should have not changed. These considerations strongly argue against a purely bottom-up stimulus-driven mechanism.

The most conservative interpretation is that practice-related decrements in visual cortex depend on the integrity of frontal-occipital connections, which convey top-down signals from frontal cortex. Top-down frontal processes may be related to the selection of relevant words and/or the suppression of competing lexical items. In the absence of left frontal cortex, selectivity is lost in left occipital cortex. This interpretation is consistent with the attenuation of word-related potentials (N170) during lexical decision or word recognition in patients with frontal cortex damage (Swick and Kinght, 1998). It is also consistent with combined lesion and single unit experiments in monkey that show neural activation in infero-temporal cortex by top-down signals from frontal cortex conveying information on semantic categorization during visual stimulus–stimulus association (Tomita et al., 1999).

Implication for Recovery of Language after Stroke

The association between word retrieval learning and the modulation of compensatory right frontal-occipital networks strongly suggests that right hemisphere mechanisms are task relevant at the chronic stage after left IFG damage and are amenable to change through practice. This conclusion is consistent with the observation that a second stroke in the right hemisphere abolishes whatever language has recovered following a first left hemisphere stroke (Basso et al., 1989; Cappa and Vallar, 1992). It is also consistent with a study by Musso et al. (1999) in chronic aphasics with lesions of the left posterior superior temporal gyrus. They reported a positive correlation between blood flow in right posterior superior temporal gyrus and improvement in auditory comprehension (measured outside the scanner) induced by specific training. Finally, Leff et al. (2002) found a parametric response increment to word stimuli in homologous right temporal cortex after left temporal infarction.

While these results point to right hemisphere mechanisms, other studies suggest a role of left hemisphere regions in language recovery. Heiss and colleagues (1999) reported, in a longitudinal study of frontal/subcortical patients, that recovery on auditory comprehension (measured outside of the scanner) positively correlates with restoration of activity in left temporal cortex. In another study, restoration of left temporal activity was found to be inversely correlated with activation in right temporal cortex (Karbe et al., 1998).

In this study, we found several subjects (P1–P3) with small lesions and evidence of perilesional activation near the left frontal stroke. These patients had the highest overall performance on word stem completion. In our previous study, we also found that two patients with the best language recovery and performance on word retrieval also had the smallest lesions and activated tissue near the lesion in left frontal cortex (Rosen et al., 2000). Therefore, it appears that the presence of perilesional activity (and small lesions) at the chronic stage qualitatively correlates with excellent recovery and high word retrieval performance.

In conclusion, the available evidence indicates a role

for both activation of homologous contralesional cortex and restoration of activity of left hemisphere regions (perilesionally and at distance) as viable mechanisms for language recovery. The compensatory activity in the right hemisphere may reflect a switch in strategy or a reweighting of activity within bilateral networks that are left lateralized in the intact brain. An important contribution of this study is to show that compensatory pathways are amenable to plasticity through learning. This is an important physiological principle with implications for rehabilitative and pharmacological approaches to the treatment of stroke.

Experimental Procedures

Subjects

14 control subjects (6 male), mean age 38.7, and 8 patients (2 male), mean age 48.6, participated in the study. Informed consent was obtained from each subject following local Institutional Review Board (IRB) guidelines. All participants were strongly right handed as measured by the Edinburgh handedness inventory and had normal or corrected-to-normal visual acuity. Inclusion criteria were: (1) a single left hemisphere vascular lesion involving the left inferior frontal gyrus and operculum, with possible extension to neighboring cortex and white matter and (2) an interval of at least 6 months since the acute event. Exclusion criteria were: (1) any other lesion on CT or MRI of the brain, except for small subcortical lacunes (up to two were allowed), (2) stenosis greater than 50% of the lumen of the internal carotid artery by Doppler ultrasonography or cerebral angiography, (3) impairment of verbal comprehension preventing understanding of instructions, and/or (4) any history or clinical evidence of dementia based on an examination by a board certified neurologist (M.C.). All patients were evaluated with either the Western Aphasia Battery or the Boston Diagnostic Aphasia Examination. All the subjects that participated in this study performed the behavioral and fMRI sessions on the same day, and all completed the whole fMRI study.

Apparatus, Stimuli, and Behavioral Analysis

Stimuli were generated by an Apple Power Macintosh computer and projected onto a screen at the head of the magnet bore by a Sharp LCD projector. Subjects viewed the stimuli through a mirror attached to the head coil. Stimuli were white on a black background, displayed at the fovea for 3.5 s. Each word stem was followed by a random interstimulus interval (3.58, 5.94, or 8.30 s). Each list of word stems contained 40 items in the behavioral session and 49 items in the fMRI session. The order of stimulus presentation was randomized in each block (fMRI run). Each word stem was presented only once per block. Percentage errors (including no responses, incorrect responses) and mean vocal RTs were computed in each subject in each block of trials. These data were analyzed with random-effect ANOVAs on group (controls, patients) and block order (blocks 1–8).

fMRI Scan Acquisition and Data Analysis

MR images were acquired on a 1.5 Tesla Siemens Vision. An asymmetric spin-echo, echoplanar sequence was used to measure blood oxygenation level-dependent (BOLD) contrast (TR = 2.36 s, TE = 50 ms, flip angle = 90°). Each run consisted of 128 frames, with each frame including 16 contiguous 8 mm axial slices (3.75 × 3.75 mm in-plane resolution). Eight runs were acquired in each subject. Anatomical imaging included a sagittal T1-weighted MP-RAGE scan (TR = 97 ms, TE = 4 ms, flip angle = 12°, TI = 300 ms). Functional data were realigned within and across runs to correct for head movement, and coregistered with anatomical data. Whole brain normalization was applied to equate mode signal intensity across subjects. Data were not normalized across groups. Linear detrending was applied to eliminate drift in the MR signal. In each subject, hemodynamic responses (eight frames long) were estimated at the voxel level using the general linear model (Ollinger et al., 2001). The individual time-points of each hemodynamic response were used to compute voxel-level or regional ANOVAs using a random-effect model. F maps at the voxel-wise level were corrected for multiple comparisons using a Monte-Carlo based threshold, and converted to equivalent Z statistics. Regions of interest (ROI) were selected on the multiple comparison corrected image by including for each region all voxels above the significant threshold ($z = 3$ at cluster size of 45 voxels). Group differences in the BOLD signal during word stem completion was analyzed with a group (controls, patients) × MR frame (frames 1–8) voxel-wise ANOVA on novel stimuli only (fMRI runs 1, 6, 7, 8). In each group, the effect of practice was evaluated with items (novel, repeat) × MR frame (frames 1–8) regional ANOVAs on novel items (scans 1, 6, 7, and 8) and on repeated items in the last scan (scan 5). In each group the regions of interest (ROIs) were selected on the voxel-wise main effect (MR frame) multiple comparison-corrected F image. This image identifies all significant regions of signal change independently of practice. To compare the effect of practice between groups, we used group (controls, patients) × item (novel, repeat) × MR frame (frames 1–8) regional ANOVAs on time courses extracted from those few ROIs showing a significant practice effect in each group. Since this analysis could be potentially biased by the selection of regions in each group, we also ran a voxel-wise 1-between: group (controls, patients) × 2-within: practice (novel, repeat) × MR frame (1–8), which was unbiased by the selection of the region.

For Figure 1, each patient's lesion extent was manually segmented (using Analyze and AVW 4.0 [Mayo Foundation for Medical Education and Research, Rochester, MN]) and represented in all or none fashion after atlas transformation of the T1 weighted (MP-RAGE) anatomical data.

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References

Alexander, M.P. (1997). Aphasia: clinical and anatomic aspects. In Behavioral Neurology and Neuropsychology, T.E. Feinberg and M.J. Farah, eds. (St. Louis: McGraw Hill), pp. 133–152.

Alexander, M.P., Hiltbrunner, B., and Fischer, R.S. (1989). Distributed anatomy of transcortical sensory aphasia. Arch. Neurol. *46*, 885–892.

Balota, D.A. (1994). Visual word recognition: the journey from features to meaning. In Handbook of Psycholinguistics, M. Gernsbacher, ed. (San Diego: Academic Press, Inc.), pp. 303–358.

Basso, A., Gardelli, M., Grassi, M.P., and Mariotti, M. (1989). The role of the right hemisphere in recovery from aphasia. Two case studies. Cortex *25*, 555–566.

Belin, P., Van Eeckhout, P., Zilbovicus, M., Remy, P., Francois, C., Guillame, S., Chain, F., Rancurel, G., and Samson, Y. (1996). Recovery from nonfluent aphasia after melodic intonation therapy: A PET study. Neurology *47*, 1504–1511.

Blumstein, S.E. (1995). The neurobiology of language. In Speech, Language, and Communication, J.L. Miller and P.D. Eimas, eds. (San Diego: Academic Press, Inc.), pp. 339–370.

Brewer, J.B., Zhao, Z., Desmond, J.E., Glover, G.H., and Gabrieli, J.D. (1998). Making memories: brain activity that predicts how well visual experience will be remembered. Science *281*, 1185–1187.

Buckner, R.L., Petersen, S.E., Ojemann, J.G., Miezin, F.M., Squire, L.R., and Raichle, M.E. (1995a). Functional anatomical studies of explicit and implicit memory retrieval tasks. J. Neurosci. *15*, 12–29.

Buckner, R.L., Raichle, M.E., and Petersen, S.E. (1995b). Dissocia-

tion of human prefrontal cortical areas across different speech production tasks and gender groups. J. Neurophysiol. *74*, 2163–2173.

Buckner, R.L., Corbetta, M., Schatz, J., Raichle, M.E., and Petersen, S.E. (1996). Preserved speech abilities and compensation following prefrontal damage. Proc. Natl. Acad. Sci. USA *93*, 1249–1253.

Buckner, R.L., Goodman, J., Burock, M., Rotte, M., Koutstaal, M., Schacter, D.L., Rosen, B., and Dale, A.M. (1998). Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. Neuron *20*, 285–296.

Buckner, R.L., Koustaal, W., Schachter, D.L., and Rosen, B.R. (2000). Functional MRI evidence for a role of frontal and inferior temporal cortex in amodal components of priming. Brain *123*, 620–640.

Cappa, S.F., and Vallar, G. (1992). The role of the left and right hemispheres in recovery from aphasia. Aphasiology *6*, 359–372.

Courtney, S.M., Ungerleider, L.G., Keil, K., and Haxby, J.V. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. Cereb. Cortex *6*, 39–49.

De Renzi, E., Liotti, M., and Nichelli, P. (1987). Semantic amnesia with preservation of autobiographic memory. A case report. Cortex *23*, 575–597.

Desmond, J.E., Gabrieli, J.D.E., and Glover, G.H. (1998). Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. Neuroimage *7*, 368–376.

Dronkers, N.F., Redfern, B.B., and Knight, R.T. (2000). The neural architecture of language disorders. In The New Cognitive Neurosciences, M.S. Gazzaniga, ed. (Cambridge, MA: MIT Press), pp. 949–958.

Gabrieli, J.D., Poldrack, R.A., and Desmond, J.E. (1998). The role of left prefrontal cortex in language and memory. Proc. Natl. Acad. Sci. USA *95*, 906–913.

Gabrieli, J.D.E., Desmond, J.E., Demb, J.B., Wagner, A.D., Stone, M.V., Vaidya, C.J., and Glover, G.H. (1996). Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. Psychol. Sci. *7*, 278–283.

Gazzaniga, M.S. (1970). The Bisected Brain (New York: Appleton).

Gazzaniga, M.S. (1983). Right hemisphere language following brain bisection: a 20-year perspective. Am. Psychol. *38*, 525–537.

Goodglass, H., Quadfasel, F.A., and Timberlake, W. (1964). Phrase length and the type and severity of aphasia. Cortex *1*, 133–153.

Gowers, W.R. (1887). Lectures on the Diagnosis of the Diseases of the Brain (Philadelphia: P. Blakiston, Son & Co.).

Heiss, W.D., Kessler, J., Thiel, A., Ghaemi, M., and Karbe, H. (1999). Differential capacity of left and right hemispheric areas for compensation of post-stroke aphasia. Ann. Neurol. *45*, 430–438.

Hodges, J.R., and Graham, K.S. (2001). Episodic memory: insights from semantic dementia. Philos. Trans. R. Soc. Lond. B Biol. Sci. *356*, 1423–1434.

Karbe, H., Thiel, A., Weber-Luxenburger, G., Herholz, K., Kessler, J., and Heiss, W.-D. (1998). Brain plasticity in poststroke aphasia: what is the contribution of the right hemisphere? Brain Lang. *64*, 215–230.

Kelley, W.M., Miezin, F.M., McDermott, K.B., Buckner, R.L., Raichle, M.E., Cohen, N.J., Ollinger, J.M., Akbudak, E., Conturo, T.E., Snyder, A.Z., and Petersen, P.E. (1998). Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. Neuron *20*, 927–936.

Kertesz, A., and McCabe, P. (1977). Recovery patterns and prognosis in aphasia. Brain *1*, 1–18.

Kinsbourne, M. (1971). The minor cerebral hemisphere as a source of aphasic speech. Arch. Neurol. *25*, 302–306.

Kinsbourne, M. (1977). Hemi-neglect and hemisphere rivalry. In Hemi-Inattention and Hemispheric Specialization, E.A. Weinstein and R.L. Friedland, eds. (New York: Raven Press), pp. 41–52.

Knight, R.T., Scabini, D., and Woods, D.L. (1989). Prefrontal cortex gating of auditory transmission in humans. Brain Res. *504*, 338–342.

Konishi, S., Donaldson, D.I., and Buckner, R.L. (2001). Transient activation during block transition. Neuroimage *13*, 364–374.

Leff, A., Crinion, J., Scott, S., Turkheimer, F., Howard, D., and Wise, R. (2002). A physiological change in the homotopic cortex following left posterior temporal lobe infarction. Ann. Neurol. *51*, 553–558.

Miller, E.K., and Desimone, R. (1994). Parallell neuronal mechanisms for short-term memory. Science *263*, 520–522.

Miller, E.K., Erickson, C.A., and Desimone, R. (1996). Neural mechanisms of visual working memory in prefrontal cortex of the macaque. J. Neurosci. *16*, 5154–5167.

Mohr, J.P., Pessin, M.S., Finkelstein, S., Funkenstein, H.H., Duncan, G.W., and Davis, K.R. (1978). Broca aphasia: pathologic and clinical. Neurology *28*, 311–324.

Musso, M., Weiller, C., Kiebel, S., Muller, S.P., Bulau, P., and Rijntjes, M. (1999). Training-induced brain plasticity in aphasia. Brain *122*, 1781–1790.

Ojemann, J.G., Buckner, R.L., Akbudak, E., Snyder, A.Z., Ollinger, J.M., Mckinstry, R.C., Rosen, B.R., Petersen, S.E., Raichle, M.E., and Conturo, T.E. (1998). Functional MRI studies of word stem completion: reliability across laboratories and comparison to blood flow imaging with PET. Hum. Brain Mapp. *6*, 203–215.

Ollinger, J.M., Shulman, G.L., and Corbetta, M. (2001). Separating processes within a trial in event-elated functional MRI. Neuroimage *13*, 210–217.

Petersen, S.E., and Fiez, J.A. (1993). The processing of single words studied with positron emission tomography. Annu. Rev. Neurosci. *16*, 509–530.

Petersen, S.E., Fox, P.T., Posner, M.I., Mintun, M., and Raichle, M.E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature *331*, 585–589.

Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., and Gabrieli, J.D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. Neuroimage *10*, 15–35.

Price, C.J. (2000). The anatomy of language: contributions from functional neuroimaging. J. Anat. *197*, 335–359.

Raichle, M.E., Fiez, J.A., Videen, T.O., MacLeod, A.K., Pardo, J.V., Fox, P.T., and Petersen, S.E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb. Cortex *4*, 8–26.

Rainer, G., and Miller, E.K. (2000). Effects of visual experience on the representation of objects in the prefrontal cortex. Neuron *27*, 179–189.

Rijntjes, M., and Weiller, C. (2002). Recovery of motor and language abilities after stroke: the contribution of functional imaging. Prog. Neurobiol. *66*, 109–122.

Rosen, H.J., Petersen, S.E., Linenweber, M., Snyder, A.Z., White, D., Chapman, L., Dromerick, J.A., Fiez, J.A., and Corbetta, M. (2000). Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology *55*, 1883–1894.

Swick, D., and Kinght, R.T. (1998). Cortical lesions and attention. In The Attentive Brain, R. Parasuraman, ed. (Cambridge, MA: MIT Press), pp. 143–162.

Thompson-Schill, S.L., Swick, D., Farah, M.J., D'Esposito, M., Kan, I.P., and Knight, R.T. (1998). Verb generation in patients with focal frontal lesions: a neuropsychological test of neuroimaging findings. Proc. Natl. Acad. Sci. USA *22*, 15855–15860.

Thompson-Schill, S.L., D'Esposito, M., and Kan, I.P. (1999). Effects of repetition and competition on activity in left prefrontal cortex during verb generation. Neuron *23*, 513–522.

Thulborn, K.R., Carpenter, P.A., and Just, M.A. (1999). Plasticity of language-related brain function during recovery from stroke. Stroke *30*, 749–754.

Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I., and Miyashita, Y. (1999). Top-down signal from prefrontal cortex in executive control of memory retrieval. Nature *401*, 699–703.

Tulving, E., and Schacter, D.L. (1990). Priming and human memory systems. Science *247*, 301–306.

Vandenberghe, R., Price, C., Wise, R., Josephs, O., and Frackowiak, R.S. (1996). Functional anatomy of a common semantic system for words and pictures. Nature *383*, 254–256.

Wagner, A.D., Schacter, D.L., Rotte, M., Koustaal, W., Maril, A., Dale, A.M., Rosen, B.R., and Buckner, R.L. (1998). Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science *281*, 1188–1191.

Wernicke, K. (1908). The symptom complex of aphasia. In Modern Clinical Medicine: Diseases of the Nervous System, E.D. Church, ed. (New York: Appleton, Century, and Crofts).

Wise, R., Chollet, F., Hadar, U., Friston, K., Hoffner, E., and Frackowiak, R. (1991). Distribution of cortical neural networks involved in word comprehension and word retrieval. Brain *114*, 1803–1817.

Yamaguchi, S., and Knight, R.T. (1990). Gating of somatosensory input by human prefrontal cortex. Brain Res. *521*, 281–288.

Zaidel, E., and Peters, A.M. (1981). Phonological encoding and ideographic reading by the disconnected right hemisphere: two case studies. Brain Lang. *14*, 205–234.